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(71) Applicant (for all designated States except US): CIBA
SPECIALTY CHEMICALS HOLDING INC. [CH/CH];
Klybeckstrasse 141, CH-4057 Basel (CH).

(72) Inventors; and

(75) Inventors/Applicants (for US only): BLATTER,
Fritz [CH/CH]; Oerinstrasse 67, CH-4153 Reinach
(CH). VAN DER SCHAAF, Paul Adriaan [NL/FR];
1, Rue Du Muguet, F-68220 Hagenthal-le-haut (FR).
SZELAGIEWICZ, Martin [CH/CH]; Christoph
Merian-strasse 1, CH-4142 Münchenstein (CH).

(74) Common Representative: CIBA SPECIALTY CHEM-
ICALS HOLDING INC.; Patent Department, Klybeck-
strasse 141, CH-4057 Basel (CH).

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(54) Title: CRYSTALLINE FORMS OF ROSUVASTATIN CALCIUM SALT

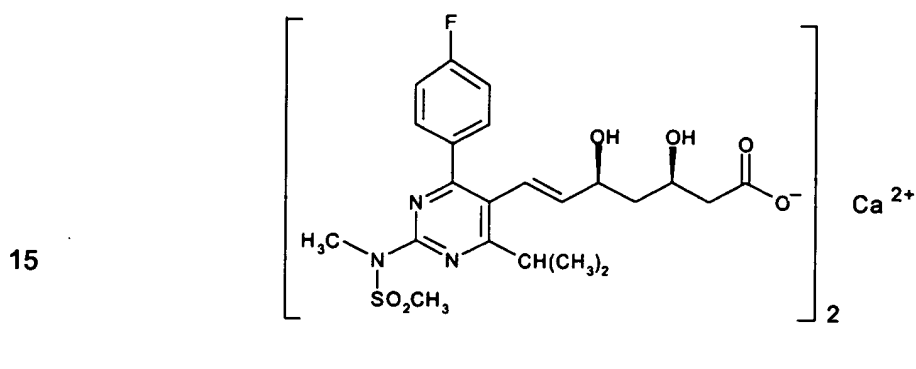
(57) Abstract: Bis [(E) -7- [4- (4-fluorophenyl) -6-isopropyl-2- [methyl (methylsulfonyl) amino] pyrimidin-5-yl] - (3R, 5S) -3, 5-dihydroxyhept-6-enoic acid] (also known as rosuvastatin) calcium salt and hydrates can exist in new crystal forms B and C. These crystal forms provide a higher diversity on crystalline materials to optimize manufacture, formulation and biological efficiency.

Crystalline forms of rosuvastatin calcium saltField of the Invention:

The present invention relates to crystalline forms of rosuvastatin calcium. This invention also relates to processes for preparing crystalline forms of rosuvastatin calcium. This invention also relates to compositions comprising of crystalline forms of rosuvastatin calcium and a pharmaceutically acceptable carrier, and to methods of using crystalline forms of rosuvastatin calcium and compositions thereof to treat a disease condition wherein inhibition of HMG CoA reductase is beneficial.

Background to the Invention:

Rosuvastatin calcium is known by its chemical name as bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt of formulae (1)



which is known to inhibit the HMG-CoA reductase, and subsequently suppress the biosynthesis of cholesterol. Rosuvastatin calcium is useful in the treatment of hypercholesterolemia, hyperlipoproteinemia, and atherosclerosis. Rosuvastatin calcium may form hydrates with a varying content of water.

20

EP-A1-0 521 471 describes in example 7 the preparation of rosuvastatin calcium in powder form. Rosuvastatin sodium is dissolved in water at room temperature and an aqueous calcium chloride solution is added dropwise. The collected precipitate is an amorphous powder. US-B2-6,777,552 discloses the preparation of rosuvastatin calcium through hydrolysis of methyl 7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R,5S)-3,5-dihydroxy-(E)-6-heptanoate with calcium hydroxide in a water / ethanol solution.

25

The compound is not isolated from the solution to characterize an amorphous or crystalline state.

- In WO 00/42024 is disclosed a crystalline form, hereafter referred to as form A of bis[(E)-7-
5 [4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt and hydrates thereof, which are prepared by dissolving the amorphous form in a mixture of water and an organic solvent such as acetone or acetonitrile under heating and then cooling the solution to precipitate crystalline form A.
- 10 Crystalline forms often show desired different physical and/or biological characteristics which may assist in the manufacture or formulation of the active compound, to the purity levels and uniformity required for regulatory approval. Crystalline forms of such active compounds may also possess improved pharmacological characteristics, for example, improved bioavailability, and therefore, novel crystalline forms offer enhanced possibilities to modulate and design
15 improved drug products. There exists therefore a need for other crystal forms than form A of bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt to have a sufficient diversity on crystalline materials to optimize manufacture, formulation and biological efficiency.

20 Summary of the Invention:

This invention provides crystalline forms B and C of rosuvastatin calcium and processes for their manufacture.

- A first object of the invention is a crystalline form of bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-
25 2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt and hydrates thereof which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (Å):
30.00 (vs), 18.10 (m), 15.00 (m) and 10.00 (m);
hereinafter designated as form B.

- 30 More specifically, the present invention comprises a crystalline form of bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt and hydrates thereof, which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (Å):

- 3 -

30.0 (vs); 18.1 (m); 15.0 (m); 12.9 (w); 10.7 (vw); 10.0 (m); 9.5 (w); 8.6 (vs); 7.7 (w); 6.3 (vw); 6.00 (vw); 5.56 (vw); 4.74 (w); 4.57 (w); 4.34 (vw); 4.24 (vw); 4.02 (vw); 3.87 (w); 3.79 (w); and 3.66 (vw); hereinafter designated as form B.

- 5 Here and in the following the abbreviations in brackets mean: (vvs) = very very strong intensity; (vs) = very strong intensity; (s) = strong intensity; (m) = medium intensity; (w) = weak intensity and (vw) = very weak intensity.

10 In still another preferred embodiment, the present invention comprises a crystalline form B of bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt and hydrates thereof, which exhibits characteristic X-ray powder diffraction patterns as exhibited in Figure 1.

- 15 A second object of the invention is a process for the preparation of crystalline form B of bis-[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt and hydrates thereof which comprises
- a) dissolving at ambient temperature a rosuvastatin calcium or a hydrate thereof in water containing an anionic surfactant;
 - b) removing at ambient temperature water to reduce the volume of water to at least 30% of the volume used to dissolve rosuvastatin;
 - 20 c) stirring the obtained suspension at ambient temperature for a time sufficient to produce said form B; and
 - d) filtering off the solid.

- 25 The concentration of rosuvastatin in water may range from 0.001 to 1 percent by weight, and preferably from 0.01 to 0.8 percent by weight.

Ambient temperature means in the context of the invention a temperature range at room temperature, comprising 20 to 30 °C and preferably about 23 to 26 °C.

30

Anionic surfactants are well known and may comprise organic compounds having hydrophilic acidic groups and hydrophobic carbon residues with for example 6 to 30 and preferably 10 to 22 carbon atoms, and optionally hetero atoms such as oxygen. Examples for acidic groups are $-\text{CO}_2\text{H}$, $-\text{SO}_3\text{H}$, $-\text{OSO}_3\text{H}$ and $-\text{PO}_3\text{H}$. Examples for carbon residues are C_8 - C_{22} alkyl and

C₈-C₁₈alkylphenyl. The anionic surfactants may be used in the form of salts such as sodium or potassium salts. Preferred anionic surfactants are alkyl sulphates having for example formula C₈-C₂₂alkylOSO₃H and their sodium or potassium salts. Particularly preferred are alkyl sulphates having formula C₁₀-C₁₈alkylOSO₃H and their sodium or potassium salts. The
5 amount of used anionic surfactant may range from 0.001 to 0.5 percent by weight and preferably 0.01 to 0.2 percent by weight, referred to the amount of water.

Removal of water may be carried out applying vacuum, a flow of inert gas such as nitrogen or air, or both. The volume reduction is preferably 50%, more preferably 65% and especially
10 preferred 80% or more.

Phase equilibration in process step c) may be carried out for a time period of hours to several days, e.g. 4 hours to 20 days or 8 hours to 10 days.

15 Crystal form B is isolated after process step c) by filtering off the crystals, which may be washed then with a small amount of water and dried then, e.g. in vacuum, an inert gas flow or both at ambient temperature.

Form B can be dried below 80°C, and is obtained as a fine powder with typical particle size
20 distributions with the median size between 1 and 50 µm, preferably between 1 to 10 µm. This particle size range ensures a fast dissolution profile, while retaining the favourable handling properties in the formulation process. Form B is better soluble in water and in physiological liquids than form A but chemically and physically more stable than the amorphous form.

25 A third object of the invention is a crystalline form of bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt and hydrates thereof which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (Å) peak expressed in 2θ-values (Å), measured with a conventional powder X-ray diffractometer using Cu-Kα radiation at
30 2θ = 3.6°±2° (m):
hereinafter designated as form C.

In a further embodiment, the present invention comprises a crystalline form of bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]](3R,5S)-3,5-dihydro-

xyhept-6-enoic acid] calcium salt and hydrates thereof, which exhibits characteristic X-ray powder diffraction peaks expressed in 2θ -values ($^{\circ}$), measured with a conventional powder X-ray diffractometer using Cu-K α radiation at $2\theta = 3.6^{\circ} \pm 2^{\circ}$ (m) and at $2\theta = 19^{\circ} \pm 5^{\circ}$ (m, broad)

5 hereinafter designated as form C.

In a preferred embodiment, the present invention comprises a crystalline form C of bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt and hydrates thereof, which exhibits characteristic
10 X-ray powder diffraction patterns as exhibited in Figure 2.

It was surprisingly found that crystal form C can be prepared by phase equilibration starting with suspended amorphous rosuvastatin calcium or a hydrate thereof in an organic solvent containing a small amount of water. The organic solvent preferably provides a low solubility
15 for the amorphous rosuvastatin calcium or a hydrate thereof, which may be in the range of 0.01 to 10 mg/ml, more preferably 0.1 to 5 mg/ml and particularly 0.1 to 3 mg/ml.

A fourth object of the invention is a process for the preparation of crystalline form C of bis-[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]](3R,5S)-
20 3,5-dihydroxyhept-6-enoic acid] calcium salt and hydrates thereof which comprises

- a) suspending at ambient temperature an amorphous rosuvastatin calcium or a hydrate thereof in an organic solvent which has a low solubility for said rosuvastatin calcium or a hydrate thereof and which contains a small amount of water;
- b) heating the suspension to a temperature of at least 40 $^{\circ}$ C for a short time period;
- 25 c) cooling down thereafter the suspension to a temperature below 20 $^{\circ}$ C;
- d) stirring the suspension at the temperature of step c) for a time period of up to 4 days;
- e) raising the temperature to ambient temperature and stirring for a time period sufficient to form crystal form C at ambient temperature; and
- f) filtering off afterwards the crystalline solid from the suspension.

30

Organic solvents which have a low solubility may be selected from aliphatic alcohols, having at least 2 carbon atoms and up to 12, preferably up to 6 carbon atoms, such as ethanol, n- or i-propanol, n-, i- or t-butanol, pentanols, hexanols, octanols, decanols and dodecanols. Organic solvents which have a low solubility may also be selected from aliphatic or cycloaliphatic

hydrocarbons such as pentane, hexane, heptane, octane, petrolether, cyclohexane and methylcyclohexane. Organic solvents which have a low solubility may further be selected from aliphatic non-cyclic ethers such as diethylether, di-n- or -i-propylether, di-n-, -i- or t-butylether, methyl-propylether, methyl-n-butylether and methyl-t-butylether. Some preferred sol-
5 vents are C₂-C₄alkanols, C₅-C₈alkanes, C₆-C₈cycloalkanes, di-i-propylether and methyl-t-butylether.

Small amount of water means in the context of the invention a content of 0.01 to 20, preferably 0.1 to 10 and in particular 0.1 to 3 volume percent.

10

The suspension may be heated in process step b) to a temperature of at least 40 °C and up to 120 °C, preferably to 50 °C to 100 °C, and particularly 60 °C to 90 °C.

Short time period in process step b) may mean at least for 2 minutes and up to 30 minutes,
15 preferably up to 20 minutes and most preferably up to 5 to 10 minutes.

The suspension may be cooled in process step c) to preferably -20 °C to 15 °C and more preferably -10 °C to 10 °C.

20 The time period in process step may be for example from 12 hours up to 4 days, preferably 24 hours to 72 hours.

The time period sufficient to form crystal form C may range from 10 to 150 hours, preferably 24 to 120 hours.

25

Crystal form C is isolated after process step e) by filtering off the crystals, which may be washed then with a small amount of water and dried then, e.g. in vacuum, an inert gas flow or both at ambient temperature.

30 Form C can be dried below 80°C, and is obtained as a fine powder with typical particle size distributions with the median size between 1 and 50 µm, preferably between 1 to 10 µm. This particle size range ensures a fast dissolution profile, while retaining the favourable handling properties in the formulation process. Form C is better soluble in water and in physiological liquids than form A but chemically and physically more stable than the amorphous form.

The crystal forms B and C may be used in pharmaceutical compositions and additionally as intermediates and starting materials to produce the thermodynamically most stable form A.

Accordingly, this invention is also directed to a pharmaceutical composition comprising the
5 crystal forms B and/or C of bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl)](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt and hydrates thereof, and a pharmaceutically acceptable carrier or diluent.

The amount of crystal forms of bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl)](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt and hydrates
10 thereof substantially depends on type of formulation and desired dosages during administration time periods. The amount in an oral formulation may be from 0.1 to 200 mg, preferably from 0.5 to 100 mg, and more preferably from 1 to 50 mg.

15 Oral formulations may be solid formulations such as capsules, tablets, pills and troches, or liquid formulations such as aqueous suspensions, elixirs and syrups. Solid and liquid formulations encompass also incorporation of the crystal forms B and/or C of into liquid or solid food.

20 The crystal forms according to the invention may be directly used as powders (micronized particles), granules, suspensions or solutions, or they may be combined together with other pharmaceutically acceptable ingredients in admixing the components and optionally finely divide them, and then filling capsules, composed for example from hard or soft gelatine, compressing tablets, pills or troches, or suspend or dissolve them in carriers for suspensions, elixirs and syrups. Coatings may be applied after compression to form pills.
25

Pharmaceutically acceptable ingredients are well known for the various types of formulation and may be for example binders such as natural or synthetic polymers, excipients, lubricants, surfactants, sweetening and flavouring agents, coating materials, preservatives, dyes, thickeners, adjuvants, antimicrobial agents and carriers for the various formulation types.
30

Examples for binders are gum tragacanth, acacia, starch, gelatine, and biological degradable polymers such as homo- or co-polyesters of dicarboxylic acids, alkylene glycols, polyalkylene glycols and/or aliphatic hydroxyl carboxylic acids; homo- or co-polyamides of dicarboxylic

acids, alkylene diamines, and/or aliphatic amino carboxylic acids; corresponding polyester-polyamide-co-polymers, polyanhydrides, polyorthoesters, polyphosphazene and polycarbonates. The biological degradable polymers may be linear, branched or crosslinked. Specific examples are poly-glycolic acid, poly-lactic acid, and poly-d,l-lactide/glycolide. Other examples for polymers are water-soluble polymers such as polyoxaalkylenes (polyoxaethylene, polyoxapropylene and mixed polymers thereof, poly-acrylamides and hydroxylalkylated poly-acrylamides, poly-maleic acid and esters or -amides thereof, poly-acrylic acid and esters or -amides thereof, poly-vinylalcohol und esters or -ethers thereof, poly-vinylimidazole, poly-vinylpyrrolidon, und natural polymers like chitosan, carragenan or hyaluronic acid.

Examples for excipients are phosphates such as dicalcium phosphate.

Examples for lubricants are natural or synthetic oils, fats, waxes, or fatty acid salts like magnesium stearate.

Surfactants may be anionic, anionic, amphoteric or neutral. Examples for surfactants are lecithin, phospholipids, octyl sulfate, decyl sulfate, dodecyl sulfate, tetradecyl sulfate, hexadecyl sulfate and octadecyl sulfate, Na oleate or Na caprate, 1-acylaminoethane-2-sulfonic acids, such as 1-octanoylaminoethane-2-sulfonic acid, 1-decanoylaminoethane-2-sulfonic acid, 1-dodecanoylaminoethane-2-sulfonic acid, 1-tetradecanoylaminoethane-2-sulfonic acid, 1-hexadecanoylaminoethane-2-sulfonic acid, and 1-octadecanoylaminoethane-2-sulfonic acid, and taurocholic acid and taurodeoxycholic acid, bile acids and their salts, such as cholic acid, deoxycholic acid and sodium glycocholates, sodium caprate or sodium laurate, sodium oleate, sodium lauryl sulphate, sodium cetyl sulphate, sulfated castor oil and sodium dioctyl-sulfosuccinate, cocamidopropylbetaine and laurylbetaine, fatty alcohols, cholesterol, glycerol mono- or -distearate, glycerol mono- or -dioleate and glycerol mono- or -dipalmitate, and polyoxyethylene stearate.

Examples for sweetening agents are sucrose, fructose, lactose or aspartam.

Examples for flavouring agents are peppermint, oil of wintergreen or fruit flavours like cherry or orange flavour.

Examples for coating materials gelatine, wax, shellac, sugar or biological degradable polymers.

5 Examples for preservatives are methyl or propylparabens, sorbic acid, chlorobutanol, phenol and thimerosal.

Examples for adjuvants are fragrances.

10 Examples for thickeners are synthetic polymers, fatty acids and fatty acid salts and esters and fatty alcohols.

15 Examples for liquid carriers are water, alcohols such as ethanol, glycerol, propylene glycol, liquid polyethylene glycols, triacetin and oils. Examples for solid carriers are talc, clay, micro-crystalline cellulose, silica, alumina and the like.

The formulation according to the invention may also contain isotonic agents, such as sugars, buffers or sodium chloride.

20 The crystal forms according to the invention may also be formulated as effervescent tablet or powder, which disintegrate in an aqueous environment to provide a drinking solution.

A syrup or elixir may contain the polymorph of the invention, sucrose or fructose as sweetening agent a preservative like methylparaben, a dye and a flavouring agent.

25 The dosages include dosages suitable for oral, buccal, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), inhalant and ophthalmic administration. Although the most suitable route in any given case will depend on the nature and severity of the condition being treated, the most preferred route of the present invention is oral. The dosages may be conveniently presented in unit dosage form and prepared by any of the
30 methods well-known in the art of pharmacy.

Dosage forms include solid dosage forms, like tablets, powders, capsules, suppositories, sachets, troches and lozenges as well as liquid suspensions and elixirs. While the description is not intended to be limiting, the invention is also not intended to pertain to true

solutions of Rosuvastatin calcium whereupon the properties that distinguish the solid forms of Rosuvastatin calcium are lost. However, the use of the novel forms to prepare such solutions is considered to be within the contemplation of the invention.

5 Capsule dosages, of course, will contain the solid composition within a capsule which may be made of gelatin or other conventional encapsulating material. Tablets and powders may be coated. Tablets and powders may be coated with an enteric coating. The enteric coated powder forms may have coatings comprising phthalic acid cellulose acetate, hydroxypropylmethyl-cellulose phthalate, polyvinyl alcohol phthalate,
10 carboxymethylethylcellulose, a copolymer of styrene and maleic acid, a copolymer of methacrylic acid and methyl methacrylate, and like materials, and if desired, they may be employed with suitable plasticizers and/or extending agents. A coated tablet may have a coating on the surface of the tablet or may be a tablet comprising a powder or granules with an enteric-coating.

15 Slow release formulations may also be prepared from the crystal form according to the invention in order to achieve a controlled release of the active agent in contact with the body fluids in the gastro intestinal tract, and to provide a substantial constant and effective level of the active agent in the blood plasma. The crystal forms may be embedded for this purpose in
20 a polymer matrix of a biological degradable polymer, a water-soluble polymer or a mixture of both, and optionally suitable surfactants. Embedding can mean in this context the incorporation of micro-particles in a matrix of polymers. Controlled release formulations are also obtained through encapsulation of dispersed micro-particles or emulsified micro-droplets via known dispersion or emulsion coating technologies.

25 The crystal forms of the invention are also useful for administering a combination of therapeutic effective agents to an animal. Such a combination therapy can be carried out in using at least one further therapeutic agent which can be additionally dispersed or dissolved in a formulation.

30 The crystal forms of this invention and its formulations respectively can be also administered in combination with other therapeutic agents that are effective to treat a given condition to provide a combination therapy.

The crystal forms and the pharmaceutical composition according to the invention are highly suitable for effective treatment of disorders in connection with need of inhibiting the HMG-CoA reductase, and subsequently suppressing the biosynthesis of cholesterol. Crystalline forms B and C of Rosuvastatin calcium and hydrates thereof and pharmaceutical composition are useful in the treatment of hypercholesterolemia, hyperlipoproteinemia, and atherosclerosis.

An object of the invention is also a therapeutic method for producing an HMG-CoA reductase inhibiting effect in a mammal comprising administering to a mammal in need of such therapy, an effective amount of a crystal form B and/or C of bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt and hydrates thereof.

The polymorphic forms of the invention may be used as single component or as mixtures with other solid forms, which may be crystalline or amorphous.

As to the novel polymorphic forms of Rosuvastatin calcium it is preferred that these contain 25-100% by weight, especially 50-100% by weight, of at least one of the novel forms, based on the total amount of Rosuvastatin calcium. Preferably, such an amount of the novel polymorphic forms of Rosuvastatin calcium is 75-100% by weight, especially 90-100% by weight. Highly preferred is an amount of 95-100% by weight.

Another object of the invention is a method of delivering a crystal form of bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt and hydrates thereof to a host, comprising administering to a host an effective amount of a crystal form B and/or C according to the invention.

A further object of the invention is the use of a crystal form B and/or C of bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt and hydrates thereof for the manufacture of a medicament useful in the treatment of disorders in connection with need of inhibiting the HMG-CoA reductase, and subsequently suppressing the biosynthesis of cholesterol, and especially useful in the treatment of hypercholesterolemia, hyperlipoproteinemia, and atherosclerosis in a

mammal, such as a human; and crystal forms B and/or C according to the invention for use in medical therapy.

The following examples illustrate the invention.

5

A) Preparation of crystalline forms B and C

Example A1: Preparation of crystal form B

79 mg amorphous rosuvastatin calcium are dissolved in 20 ml of bi-distilled water containing
10 mg of sodium dodecyl sulphate. The volume of the solution is reduced then to about 3 ml
under a nitrogen gas flow of about 30 ml/min.. The resulting suspension is stirred thereafter
at 23 ± 2 °C. The crystals are filtered off, washed with 2 ml bi-distilled water and then dried in
air at room temperature. The dried crystalline solid is investigated by powder X-ray diffraction
and it shows a diffraction pattern as displayed in Figure 1.

15

Example A2: Preparation of crystal form C

49 mg amorphous rosuvastatin calcium are suspended in 3 ml t-butyl-methylether, which is
saturated with water. The suspension is heated to 75 °C for a few minutes and then cooled to
5 °C. The resulting suspension is stirred for 48 hours at 5 °C. The temperature is thereafter
raised to 23 ± 2 °C and stirring of the suspension is continued at this temperature for 5 days.
The formed white solid is filtered off, dried in air at ambient temperature and then dried in air
for about 2 hours. The dried crystalline solid is investigated by powder X-ray diffraction and it
shows a diffraction pattern as displayed in Figure 2.

25

Experimental:

Powder X-ray Diffraction (PXRD): PXRD is performed on a Philips 1710 powder X-ray dif-
fractometer using $\text{CuK}\alpha$ radiation. D-spacings are calculated from the 2θ values using the
wavelength of 1.54060 Å. Generally, 2θ values are within an error of ± 0.1 - 0.2° . The expe-
rimental error on the d-spacing values is therefore dependent on the peak location.

30

Brief description of the drawings

Figure 1 is a characteristic X-ray powder diffraction pattern of form B

Figure 2 is a characteristic X-ray powder diffraction pattern of form C

Claims:

1. A crystalline form of bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt and hydrates thereof
5 which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (Å):
30.00 (vs), 18.10 (m), 15.00 (m) and 10.00 (m);
hereinafter designated as form B.
- 10 2. A crystalline form according to claim 1, comprising bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid]
calcium salt and hydrates thereof, which exhibits a characteristic X-ray powder diffraction
pattern with characteristic peaks expressed in d-values (Å):
30.0 (vs); 18.1 (m); 15.0 (m); 12.9 (w); 10.7 (vw); 10.0 (m); 9.5 (w); 8.6 (vs); 7.7 (w); 6.3 (vw);
15 6.00 (vw); 5.56 (vw); 4.74 (w); 4.57 (w); 4.34 (vw); 4.24 (vw); 4.02 (vw); 3.87 (w); 3.79 (w);
and 3.66 (vw);
hereinafter designated as form B.
- 20 3. A crystalline form according to claim 1, comprising a crystalline form B of bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt and hydrates thereof, which exhibits a characteristic X-ray powder diffraction pattern as exhibited in Figure 1.
- 25 4. A process for the preparation of crystalline form B of bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid]
calcium salt and hydrates thereof according to claim 1, which comprises
- a) dissolving at ambient temperature a rosuvastatin calcium or a hydrate thereof in water containing an anionic surfactant;
 - b) removing water at ambient temperature to reduce the volume of water by 30% or
30 more, relative to the volume used to dissolve rosuvastatin;
 - c) stirring the obtained suspension at ambient temperature for a time sufficient to produce said form B; and
 - d) filtering off the solid.

5. A process according to claim 4, wherein the concentration of rosuvastatin in water in step a) ranges from 0.001 to 1 percent by weight.

6. A process according to claim 4, wherein ambient temperature means a temperature range at room temperature, comprising 20 to 30 °C.

7. A process according to claim 4, wherein the anionic surfactant comprises organic compounds having hydrophilic acidic groups and hydrophobic carbon residues with 6 to 30 carbon atoms, and optionally hetero atoms such as oxygen, and salts thereof.

8. A process according to claim 7, wherein the anionic surfactant comprises alkyl sulphates.

9. A process according to claim 8, wherein the anionic surfactant comprises alkyl sulphates having formula $C_8-C_{22}alkylOSO_3H$.

10. A process according to claim 4, wherein the amount of anionic surfactant ranges from 0.001 to 0.5 percent by weight, referred to the amount of water.

11. A process according to claim 4, wherein the phase equilibration in process step c) is carried out for a time period of hours to several days.

12. A crystalline form of bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)-amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt and hydrates thereof which exhibits a characteristic X-ray powder diffraction pattern peak expressed in 2θ -values (°), measured with a conventional powder X-ray diffractometer using Cu-K α radiation at $2\theta = 3.6^\circ \pm 2^\circ$ (m):

hereinafter designated as form C.

13. A crystalline form of bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)-amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt and hydrates thereof according to claim 12, which exhibits characteristic X-ray powder diffraction peaks expressed in 2θ -values (°), measured with a conventional powder X-ray diffractometer using Cu-K α radiation at

$2\theta = 3.6^\circ \pm 2^\circ$ (m) and at $2\theta = 19^\circ \pm 5^\circ$ (m, broad)

hereinafter designated as form C.

14. A crystalline form C of bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)-
5 amino]pyrimidin-5-yl]](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt and hydrates thereof, which exhibits a characteristic X-ray powder diffraction pattern as exhibited in Figure 2.

15. A process for the preparation of crystalline form C of bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt and hydrates thereof according to claim 12, which comprises

- 10 a) suspending at ambient temperature an amorphous rosuvastatin calcium or a hydrate thereof in an organic solvent which has a low solubility for said rosuvastatin calcium or a hydrate thereof and which contains a small amount of water;
- b) heating the suspension to a temperature of at least 40 °C for a short time period;
- c) cooling down thereafter the suspension to a temperature below 20 °C;
- 15 d) stirring the suspension at the temperature of step c) for a time period of up to 4 days;
- e) raising the temperature to ambient temperature and stirring for a time period sufficient to form crystal form C at ambient temperature; and
- f) filtering off afterwards the crystalline solid from the suspension.

20 16. A process according to claim 15, wherein the solubility of the organic solvent is in the range of 0.01 to 10 mg/ml.

17. A process according to claim 15, wherein organic solvent is selected from the group of aliphatic alcohols, having at least 2 and up to 12 carbon atoms, aliphatic or cycloaliphatic hydrocarbons and aliphatic non-cyclic ethers.
25

18. A process according to claim 15, wherein the amount of water in the solvent is 0.01 to 20 volume percent.

30 19. A pharmaceutical composition comprising the crystal forms B and/or C of bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt and hydrates thereof, and a pharmaceutically acceptable carrier or diluent.

20. A therapeutic method for producing an HMG-CoA reductase inhibiting effect in a mammal comprising administering to a mammal in need of such therapy, an effective amount of a crystal form B and/or C of bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt and hydrates thereof.

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21. A method of delivering a crystal form of bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt and hydrates thereof to a host, comprising administering to a host an effective amount of a crystal form B and/or C according to the invention.

10

22. Use of a crystal form B and/or C of bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt and hydrates thereof for the manufacture of a medicament useful in the treatment of disorders in connection with need of inhibiting the HMG-CoA reductase, and subsequently suppressing the biosynthesis of cholesterol.

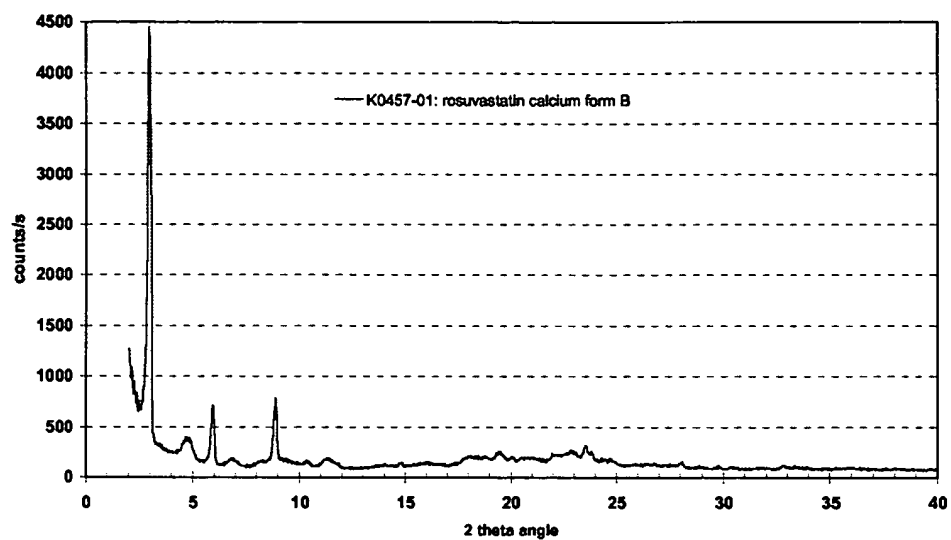
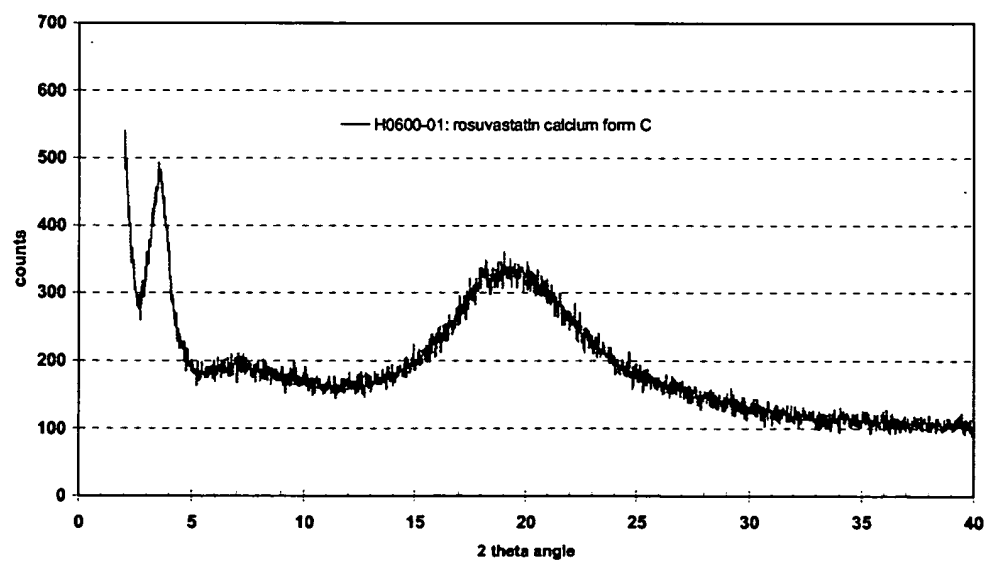
15

23. Use according to claim 22 for the manufacture of a medicament useful in the treatment of hypercholesterolemia, hyperlipoproteinemia, and atherosclerosis in a mammal, such as a human.

20

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1 / 1

Fig. 1Fig. 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/050351

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D239/42 A61K31/505 A61P3/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2006/035277 A (RANBAXY LABORATORIES LIMITED; RAFEEQ, MOHAMMAD; DE, SHANTANU; SATHYANA) 6 April 2006 (2006-04-06) figure 1	12-23
P,X	WO 2005/077916 A (RANBAXY LABORATORIES LIMITED; KUMAR, YATENDRA; RAFEEQ, MOHAMMAD; DE, S) 25 August 2005 (2005-08-25) figure 6	12-23
X	WO 00/42024 A (ASTRAZENECA UK LIMITED; TAYLOR, NIGEL, PHILLIP) 20 July 2000 (2000-07-20) cited in the application the whole document	1-3, 19-23

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *Z* document member of the same patent family

Date of the actual completion of the international search

26 April 2006

Date of mailing of the international search report

03/05/2006

Name and mailing address of the ISA/
European Patent Office, P.B. 5818 Patentaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Johnson, C

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 20,21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.2

Claims Nos.: 12-18, 19-23(part)

Claim 14 relates to a crystalline form C of rosuvastatin calcium and hydrates thereof, which exhibits a characteristic X-ray powder diffraction pattern as exhibited in Figure 2. Thus the technical features of this claim are a) that it is rosuvastatin calcium b) that it is crystalline and c) that it has the X-ray powder diffraction pattern shown in Figure 2. However, the powder diffraction pattern in Figure 2 is not a pattern characteristic of a crystalline material: the low intensity and extreme breadth of the "peaks" in this pattern indicate that the material is to a large extent amorphous. Indeed, comparison of this pattern with X-ray powder diffraction patterns of rosuvastatin calcium described as being amorphous (see e.g. W02006/035277 Figure 1; W02005/077916, Figure 6) confirm that the material giving the X-ray powder diffraction pattern in Figure 2 is substantially identical with this already known amorphous form. Claim 14 is thus contradictory, as it claims a crystalline material which exhibits a non-crystalline X-ray powder diffraction pattern. Furthermore, as the characterizing features of both claims 12 and 13 are clearly based on the X-ray powder diffraction pattern of Figure 2, as well as on the fact that the compound must be crystalline, these claims are also contradictory for the same reason. As claims 15-18 refer to methods for preparing the "crystalline" form C, which apparently exhibits a non-crystalline X-ray powder diffraction pattern, these claims are also considered to be contradictory, as are claims 19-23 insofar as they relate to compounds of crystalline form C.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/050351

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 12-18, 19-23(part)
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 20,21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 12-18, 19-23(part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2006/050351

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